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Effects of baroreceptor stimulation and opioids on the auditory startle reflex

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Abstract

We examined (a) whether carotid baroreceptor stimulation attenuates the auditory startle response and its modulation by preceding affective pictures, and (b) whether these effects are mediated by endogenous opioids. Seventy-eight young normotensive adults with or without a parental history of hypertension received brief exposures to affective pictures and noise bursts during phasic manipulation of the carotid baroreceptors. In each participant, opioids were blocked by naltrexone in half of the sessions. Baroreceptor stimulation had a strong dampening effect on the startle response. This effect was not influenced by opioid blockade, sex, or parental history of hypertension. No baroreceptor effects were obtained regarding ratings of the affective pictures or startle modulation by the pictures. The baroreceptor stimulation effects seem to be mediated by the basal primary acoustic startle circuit rather than by higher affective circuits.

Descriptors: Startle response, Affective modulation, Baroreceptor stimulation, Hypertension, Endogenous opioids

Elevated blood pressure has been repeatedly associated with diminished sensitivity to painful physical stimulation. This has been demonstrated for electrical (Zamir & Shuber, 1980), thermal (Sheps et al., 1992), and finger pressure pain stimulation techniques (Bruehl, Carlson, & McCubbin, 1992). An inverse relationship between blood pressure and perceived painfulness of physical stressors has also been found in normotensive samples (Bruehl et al., 1992; Page & France, 1997). This relationship has been confirmed in studies conducted on animals, usually applying within-subject designs in which blood pressure was raised artificially (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979; Randich & Maixner, 1984; Zamir & Segal, 1979), as well as in numerous studies on human subjects, which were based on between-subject differences in blood pressure level (Bruehl et al., 1992; Sheps et al., 1992; Zamir & Shuber, 1980; for reviews, see France, 1999; Ghione, 1996). Despite some conflicting findings (France, Ditto, & Adler, 1991; Rau et al., 1994), evidence suggests that this relationship, at least in part, may be the result of inhibitory baroreceptor effects on the central nervous system (Droste et al., 1994; Dworkin et al., 1979; Elbert, Rockstroh, Lutzenberger, Kessler, & Pietrowsky, 1988; Randich & Maixner, 1984; for a review, see Rau & Elbert, 2001). In these studies, lower pain sensitivity as a result of baroreceptor stimulation has usually been obtained in within-subject designs using artificial stimulation of baroreceptors by mechanical or pharmacological means. Recently, evidence has been found that also natural baroreceptor stimulation occurring during the systolic phase of the heart cycle has dampening effects on pain processing (Edwards, Ring, McIntyre, & Carroll, 2001). These baroreceptor effects have been suggested to be present also in normotensive samples with enhanced risk for hypertension (Elbert et al., 1988; France, 1999; Rau & Elbert, 2001).

Based on the early findings, the operant conditioning of hypertension hypothesis has been proposed by Dworkin et al. (1979). Given its pain relieving and presumably general aversiveness dampening properties, the baroreceptor stimulation mechanism may reinforce blood pressure elevations that may generalize to a wide range of potentially painful and stressful situations. Thus, phasic blood pressure increases may be understood as a learned coping mechanism. As a consequence of this mechanism, frequent exposure to potentially stressful situations may contribute to the development of essential hypertension. However, it is not yet known whether baroreceptor stimulation results in dampening of affective appraisal of nonpainful aversive stimuli. This is an important issue, because it may be expected that in everyday life aversive stimuli other than those involving physical pain are more relevant for the learned blood pressure increases to take place. Therefore, it seems relevant to examine the effects of baroreceptor stimulation on responses to stressors other than those involving physical pain that have a measurable affective component.

The affective startle reflex paradigm (Lang, Bradley, & Cuthbert, 1990) allows for examining this reflex as a basal psychophysiological response to a nonpainful physical stressor (i.e., a

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brief loud noise). In addition, it allows for examining affective modulation of this response by preceding or background (lead) affective stimuli. When the onset of the lead stimulus is several seconds before the startle stimulus, unpleasant background stimuli have been shown to potentiate the startle response, whereas pleasant stimuli attenuate the startle response magnitude (e.g., Bradley, Lang, & Cuthbert, 1993; VanOyen Witvliet & Vrana, 1995; Vrana, Spence, & Lang, 1988). Although some prudence is required when generalizing findings from animal research on the whole-body startle reflex to human startle responses, evidence from studies in rodents has shown that a simple neural pathway involving a small number of lower brain stem nuclei is sufficient for a startle reflex to occur in response to a loud stimulus (Davis, Gendelman, Tischler, & Gendelman, 1982). Involvement of subcortical cerebral areas, including limbic structures such as the amygdala, is required for modulation of the startle response by affective stimuli (Koch, 1999).

The main aim of the present investigation was to examine whether stimulation of the baroreceptors would dampen the magnitude of (a) the startle response per se, and (b) startle response modulation by preceding affective lead stimuli. Specifically, because baroreceptor stimulation has been hypothesized to attenuate the perception or appraisal of the aversive properties of a wide range of unpleasant stimuli (Dworkin et al., 1979; Elbert et al., 1988; Nyklíček, Vingerhoets, & Van Heck, 2001), we expected baroreceptor stimulation to dampen startle potentiation by preceding negative pictures. In addition, we also expected that ratings of negative pictures would be mitigated, that is, negative pictures would be rated as less aversive during baroreceptor stimulation.

An additional aim was to examine a possible pathway by which baroreceptor stimulation may exert its effect on responses to stressors. The involvement of endogenous opioids was studied, because these peptides are known to have analgesic properties (McCubbin, 1993) and may diminish feelings of fear and anxiety (Sher, 1998). Recently, opiate withdrawal has been shown to result in enhanced fear-potentiated startle in mice (Fendt & Mucha, 2001). In addition, mutual influences between the baroreflex system and opioids have been reported (Weinstock, Schorer-Appelbaum, & Rosin, 1984). Regarding the association between blood pressure and responses to painful stimuli, several studies conducted in animals have found hypertension-related hypoalgesia to heat stimuli to be eliminated by opioid blockade (Saavedra, 1981; Sitsen & De Jong, 1983, 1984; Zamir & Segal, 1979). Humans demonstrating hypoalgesia to a hot stimulus showed increased levels of circulating β-endorphins (Sheps et al., 1992). However, in another investigation, opioid blockade did not significantly diminish the negative association between resting systolic blood pressure and cold pain ratings (McCubbin & Bruehl, 1994). Schobel et al. (1998) found a mediating role of opioids in pain responses to noxious mechanostimulation (skin fold pinching) in normotensive but not in hypertensive individuals, while Bruehl, Chung, Ward, Johnson, and McCubbin (2002) reported no effect of opioid blockade on the association between blood pressure and pain sensitivity. To our knowledge, only one study has examined the potential role of opioids in baroreceptor-mediated altered responses to aversive stimuli, specifically to a painful heat stimulus administered to rats (Maixner & Randich, 1984). Naltrexone, an opioid blocker, did not influence the analgesia induced by pharmacological cardiopulmonary baroreceptor stimulation in these rats. In conclusion, the results have been mixed regarding the involvement of opioids in the relationship between blood pressure and hypoalgesia. To our knowledge, no studies have been performed regarding opioid involvement in altered responsiveness to nonpainful stressors as a result of baroreceptor stimulation.

Finally, the role of two individual difference factors was examined, that is, that of sex and parental history of hypertension. The association between blood pressure and reduced pain sensitivity has sometimes been obtained only in male participants (Fillingim & Maixner, 1996; Bragdon et al., 2002), whereas in two other studies this relation was found in women, but not in men (al'Absi, Petersen, & Wittmers, 2002; Nyklíček, Vingerhoets, & Van Heck, 1999). In light of these discrepancies, we included participants of both sexes to examine possible gender differences. In addition, normotensive young adults with either hypertensive or normotensive parents were included in the study in order to investigate whether the hypothesized baroreceptor stimulation effects are more pronounced in individuals at elevated risk for hypertension, as suggested in previous studies (Dworkin et al., 1979; Elbert et al., 1988; Rau et al., 1994).

Method

Participants

Participants comprised students of the Faculty of Social Sciences, Tilburg University, who were screened by means of a questionnaire and blood pressure measurements. During the screening, which took place in a quiet room on the university campus, blood pressure was measured three times by a trained psychology student using an automatic digital device based on the oscillometric method (Philips HP 5330). After a 5-min rest period, three measurements were performed with periods of approximately 5 min in between, during which the potential participants completed a questionnaire containing questions on demographics: height; weight; alcohol and coffee consumption; smoking; physical exercise; presence of a chronic disease; medication use, including oral contraceptives; and parental history of hypertension, diabetes mellitus, and renal dysfunction. The parents' medical information was verified later by a brief telephone survey, as recommended by France and Page (1998). The arithmetic means of the three resting systolic and diastolic blood pressures were used as a measure of baseline blood pressure level.

The screening lasted until 41 participants were found with a parental history of hypertension (PH+): having at least one hypertensive parent, the hypertension not being concomitant with diabetes mellitus or renal dysfunction in order to exclude cases of secondary hypertension. This group was matched with 39 control subjects without hypertensive parents (PH $-$). The groups were matched on sex, age, body mass index, alcohol consumption, physical exercise, and use of oral contraceptives. Because our main aim was to examine effects of baroreceptor stimulation in healthy, normotensive individuals, exclusion criteria included systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg; self-reported use of anti-hypertensive medication, antidepressants, or tranquillizers; presence of diabetes mellitus; any form of kidney disease; a history of myocardial infarction or other heart disease; any form of substance abuse; and abnormal function of the liver, as evidenced by a plasma liver enzyme test.

At a separate session, after informed consent was obtained from the participants, a blood sample was drawn in order to check liver function by means of Alanine Amino Transferase and Gamma Glutamyl Transferase enzyme tests in participants that

Table 1. *Sample Characteristics: Means and Standard Deviations or Percentages*

Variable	No parental history of hypertension (PH−; $N = 37$)	Parental history of hypertension (PH+; $N = 41$)	t or χ^2
Systolic blood pressure	117.56 (10.68)	124.56 (17.65)	−2.08*
Diastolic blood pressure	69.55 (7.37)	72.92 (11.08)	−1.57
Percentage women	51.4%	48.8%	0.51
Percentage contraceptives	55.0%	63.2%	0.27
Percentage smoker	31.6%	37.5%	0.30
Cigarettes per day	9.46 (7.11)	13.57 (8.49)	−1.33
Age	21.18 (2.71)	21.20 (2.29)	−0.04
Body mass index	22.12 (3.14)	22.08 (3.23)	0.58
Alcohol consumption	6.99 (7.44)	8.01 (7.34)	−0.61
Coffee consumption	1.31 (1.41)	1.54 (1.86)	−0.62
Physical exercise	2.58 (1.88)	2.18 (2.26)	0.86

Notes: Percentage contraceptives refers to the percentage of women using oral contraceptives; cigarettes per day is restricted to smokers only; alcohol consumption reflects the number of glasses of alcohol consumed per week; physical exercise is in hours per week; * = $p < .05$.

did not meet any of the other exclusion criteria. Elevated levels of these enzymes indicate potentially reduced ability of the liver to excrete toxic and waste products. None of the participants had to be excluded because of abnormal values. These procedures resulted in 41 PH+ (20 women) and 39 PH− (19 women) individuals, who were invited for the final laboratory protocol and who received 80 DFL (about $40) or course credit for participation. The study has been approved by the Medical Ethics Committee of the TweeSteden Hospital in Tilburg.

Because of refusal to participate a second time as a result of serious nausea during the first session ($N = 1$), and inadequate operation of the equipment due to a software problem ($N = 1$), data of 2 participants (men from the PH− group) were discarded from the analyses. These exclusions did not have an effect on the comparability of the groups. No significant differences between the PH− and PH+ groups were found on any of the matching variables (all $ps \geq .20$; Table 1). The participants were all Caucasian, between 18 and 28 years of age ($M = 21.19$, $SD = 2.51$), 50% of whom were women (19 PH− and 20 PH+). PH+ participants did have higher systolic blood pressures ($M = 124.56$, $SD = 17.65$) than participants without a parental history of hypertension ($M = 117.56$, $SD = 10.68$, $t[76] = -2.08$, $p < .05$).

Affective Pictures

The affective pictures used in the present study were drawn from the International Affective Picture System collection (Lang, Bradley, & Cuthbert, 1999). This collection contains a widely used and well-validated set of photographs differing on the dimensions of valence (the degree of pleasantness or unpleasantness) and arousal. Given the fact that the baroreceptors were stimulated phasically within each heart cycle, picture presentation times had to be limited to 100 ms. Therefore, a pilot study was performed first in order to select two sets of pictures that had extreme scores on the valence dimension (very unpleasant or very pleasant) with comparable arousal scores when viewed for 100 ms only. Ten normal adult volunteers (5 women and 5 men) viewed 88 pictures that have been shown to have extremely high and low scores on the valence dimension (Lang et al., 1999). The pictures were presented for 100 ms and were subsequently rated on the dimensions of valence, arousal, and clarity (9-point scales). Based on these scores, together with previous data on valence and arousal (Lang et al., 1999), we selected 32 extremely positive (mainly sports and erotic scenes) and 32 extremely negative pictures (mainly scenes depicting injuries and violence) that had comparable arousal scores and that did not score below 4.0 on picture clarity (scale ranged from 1, *completely unclear*, to 9, *completely clear*). Sets of positive pictures appeared to be somewhat different for men and women, especially regarding erotic scenes (having a relatively stronger explicit content for men and a relatively more romantic content for women).[1] The sets did not differ regarding valence, arousal, or clarity ratings between men and women (all $t[8] < 1.35$, $p > .10$).

Baroreceptor Stimulation

Baroreceptor manipulation was performed by applying the well-validated Phase Related External Suction (PRES) technique (Rau, Elbert, Geiger, & Lutzenberger, 1992). This technique relies on the fact that arterial baroreceptors, located in the wall of the carotid sinus and the aortic arch, are stretch receptors. Blood pressure elevation increases the diameter of blood vessels, which in turn activates baroreceptors that elicit the cardiovascular baroreflex. Because the carotid sinus is an important area of arterial baroreceptors, this effect can be augmented or inhibited by using a cuff around the neck in which pressure can be increased by blowing air into it or decreased by sucking air out of it. Suction dilates the carotid artery and therefore stimulates the carotid baroreceptors. Blowing has the opposite effect and hence inhibits baroreceptor stimulation. The PRES technique is based on the fact that baroreceptors are more sensitive to short-term changes of dilation than to long-term levels of dilation. Baroreceptors are naturally stimulated during the systolic phase of the heart cycle, during which the vessels are dilated. Applying negative cuff pressure simultaneously with the systolic pulse hence additionally stimulates the baroreceptors. Applying the same negative cuff pressure during the diastolic phase of the heart

[1]The following IAPS pictures were used in the present study. Pictures preceded by an "M" were used only for men, those preceded by an "F" only for women). *Pleasant pictures*: 1440, 1463, 1710, 2080, F2345, M4002, M4150, M4180, M4210, M4220, M4232, M4240, M4250, F4533, F4535, F4599, M4607, 4608, F4610, F4641, M4651, M4652, F4653, F4656, 4659, 4660, M4664, 4670, M4680, 5621, F7270, F7502, 8021, M8030, 8031, 8080, M8170, 8185, 8190, F8200, F8210, 8370, F8470, 8490, F8496, 8501, F8502. *Unpleasant pictures*: M2800, 3000, 3010, 3015, 3030, M3051, 3053, 3060, 3062, 3063, 3071, 3080, 3100, 3110, 3120, 3130, 3150, 3168, 3266, 3400, F3500, 3530, 6250, 6260, 6313, 6350, 6360, 6510, F6540, 6560, 6570, 9405, 9410, 9570.

cycle counteracts diastolic vessel constriction but is not strong enough to increase vessel diameter, resulting in a much lower baroreceptor activation compared to the condition of systolic suction. A similar net effect is realized when positive pressure in the cuff is induced during the systolic phase, which counteracts natural systolic dilation, whereas positive pressure during diastole inhibits baroreceptor activation the most. Thus, the PRES technique allows for examining the effects of (a) artificial carotid baroreceptor stimulation by means of inducing negative or positive changes in neck cuff pressure, and (b) natural baroreceptor stimulation by comparing the effects between the systolic and diastolic phase of the heart cycle.

Two sorts of trials, in the present study both having a duration of 9500 ms, are typically applied: (a) baroreceptor stimulation trials, consisting of negative cuff pressure (suction) during the systolic phase (maximum phasic baroreceptor stimulation), followed by positive cuff pressure (blowing) during the diastolic phase (minimum phasic baroreceptor stimulation) of the heart cycle, and (b) control trials containing the reverse cuff pressure sequence, which is related to substantially less net baroreceptor activation (Rau et al., 1992). The two types of trials are not differentiable for a vast majority of subjects (Furedy, Rau, & Roberts, 1992), indicating that the drawback of previously applied continuous neck suction techniques—larger aversiveness experienced during suction than during blowing—has been eliminated in the present design, resulting in valid control conditions (Rau et al., 1992; see Figure 1 for an example of a baroreceptor stimulation trial).

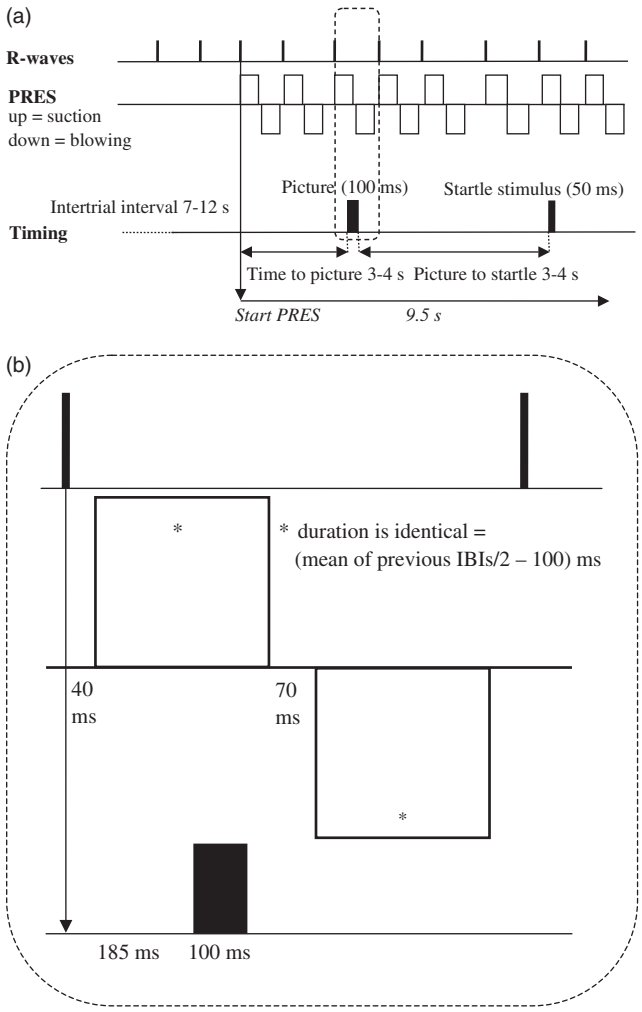

Figure 1. a: Schematic representation of one baroreceptor stimulation trial of the Phase Related External Suction (PRES) technique. Suction during systole, producing negative pressure in the cuff, is reflected by upward pulses, whereas blowing during diastole, producing positive pressure, is reflected by downward pulses. The encircled part reflects one heart cycle, the details of which are presented in panel b.

In the present study, we have made minor adjustments in the baroreceptor stimulation algorithm in order to enhance its flexibility regarding adjustment of the length of the baroreceptor stimulation pulses to the varying duration of the heart period (interbeat interval; IBI). The algorithm for the computation of the duration of the suction and blowing pulses was identical to the original one ([mean of the previous IBIs/2] – 100 ms; Rau et al., 1992), but "mean of the previous IBIs" was set to the mean of all previous IBIs during the same trial type (baroreceptor stimulation or control) and the one IBI just preceding the current heart cycle (with 40% and 60% relative weight, respectively). The onset of blowing or suction was set at 40 ms after the detection of the R-wave, with 70 ms of no stimulation between the successive suction and blowing pulses within each heart cycle (Figure 1b).

Within one trial, after a variable interval of 3–4 s from trial onset (depending on the timing of the R-waves), in the next heart period an affective picture was presented for 100 ms on a computer screen during one of the four baroreceptor manipulation conditions (systolic or diastolic phase combined with positive or negative cuff pressure; Figure 1a). The onset of the picture was at 185 ms after the onset of the neck cuff pressure change (Figure 1b), because (a) at that time approximately 70% of the final cuff pressure was achieved, and (b) stimulus duration completely fell within the suction or blowing period and the systolic or diastolic phase of the heart cycle (Rau et al., 1992). After another variable interval of 3–4 s (again depending on the timing of the R-waves), the startle stimulus (see below) was administered in half of the trials during the same baroreceptor manipulation condition as during the picture presentation using identical timing parameters.

After each trial, participants rated the valence of the picture (see below), followed by an intertrial interval of 7–12 s. The exact duration of each individual intertrial interval was randomly extracted from a distribution containing numbers between 7000 and 12,000 with a class width of 1 (ms).

Physiological Measures

As startle stimulus, we used a white noise stimulus with a 50-ms duration (1-ms rise time), generated by a Hewlett Packard 8057A Precision Noise Generator and presented through headphones (Sony CD 450). Because of some ambient noise generated by the equipment, the present stimulus was slightly louder (103 dB[A]) than stimuli used in most previous research (e.g., Lang et al., 1990; VanOyen Witvliet & Vrana, 1995), in order to ensure eyeblink response elicitation in the present context.

Standard pre-gelled electrodes (ConMed Cleartrace 1700-005) were used for measuring the electrocardiogram (ECG). They were placed (a) over the jugular notch of the sternum, between the collar bones, (b) between two ribs 4 cm under the nipple of the left breast, and (c) on the right lateral side, between two lower ribs (reference electrode). The signal was fed into a hardware R-wave detector that filtered the signal (– 3 dB

passband: 3.18–60 Hz), rectified it, and detected R-waves by triggering at the maximum slope of the ECG in the Q-R interval. When an R-wave was detected, a 100-ms square wave was produced that was digitized at 1000 Hz and served as input for the baroreceptor manipulation software program.

Two miniature (2-mm diameter) Beckman Ag/AgCl electrodes, filled with electrolyte paste, were used to obtain the electromyogram (EMG) from the orbicularis oculi muscle. The electrodes were placed in the middle of the inferior part of the left orbicularis oculi muscle having an interelectrode distance of 15 mm. The reference electrode was placed in the middle of the forehead. The raw signal was amplified and filtered using a 500 Hz low-pass and 31 Hz high-pass hardware filter (attenuation rate 46 dB per octave; cf. Van Boxtel, Boelhouwer, & Bos, 1998). Sampling frequency was 1000 Hz. Off-line, the signal was rectified and smoothed with a time constant of 10 ms (Blumenthal, 1994). A window of 50 ms before and 120 ms after startle stimulus onset was used for computing the startle eyeblink response magnitude, which was defined as the difference between the peak amplitude and the baseline level. Peak amplitude was determined within a 20–120-ms poststimulus latency window (Filion, Dawson, & Shell, 1994), and baseline level was defined as the mean level of EMG activity during the 50-ms interval just preceding startle stimulus onset. Because of excessive EMG activity in the baseline signal, 3% of the trials (the proportion was identical for PH+ and PH− groups as well as for negative pressure and positive pressure conditions) were excluded from the analyses.

Experimental Procedure

Each participant attended two experimental sessions, with an intersession interval of 1 week. Fifty milligrams of naltrexone (Nalorex, DuPont Pharma) was administered during one session and placebo during the other. The dose used is recommended by the manufacturer and by researchers in this area (McCubbin et al., 1992). Medication was taken 1 h before the experiment in order to ensure sufficiently high blood levels (McCubbin et al., 1992). The experiment was performed in a double-blind manner: Both the experimenter and the subjects did not know the nature of the substance that was taken. The order of the sessions was counterbalanced across individuals. Women not using oral contraceptives were scheduled to be in the follicular or luteal phase (determined by asking them what day of the menstrual cycle they would be in) on both sessions. This was done to assure that women were more comparable to men, as during these periods the level of estrogen and the sensitivity for aversive stimuli is lower than during the other menstrual phases (Fillingim et al., 1997).

Participants were seated in a comfortable chair that was placed in front of a computer screen in a soundproof room. The room next door, which was also soundproof, contained the baroreceptor manipulation equipment. The computer screen was used for showing the affective pictures and for rating their valence after each trial. In front of the participants, on a small stool, two buttons were placed that were used for rating the pictures. Appraised valence of each picture was measured by asking the question "To what extent did you find the picture pleasant or unpleasant?," which was scored using the face pictures as employed in the Self Assessment Manikin (Lang et al., 1999), ranging from 1 (*very unpleasant*) to 9 (*very pleasant*).

All electrodes as well as the neck cuff were attached. Headphones were placed, the door was closed, and the experimenter took a seat in an adjacent, separate room and started the experiment that lasted for approximately 100 min. The session started with 16 baroreceptor manipulation trials without pictures or startle probes in order to habituate subjects to the cuff pressure changes. In addition, these neutral trials were used to examine the cardiovascular effectiveness of the present slightly modified PRES procedure. Then, six practice trials were initiated that included the presentation of emotional pictures, three startle stimuli, and subsequent ratings of the pictures. After these training trials, the experimental part started, containing 128 trials: 16 trials for every one of the eight conditions (two mechanical baroreceptor manipulation conditions × two heart cycle phases × two valence categories of the pictures). This implies that every picture was presented twice during each session. It has been shown that presenting the same pictures several times does not diminish test–retest reliability of overall startle reflex magnitude and of modulation of the startle reflex along the valence dimension (Larson, Ruffalo, Nietert, & Davidson, 2000). Sixteen blocks of these eight conditions were presented in counterbalanced sequences: Across these blocks each condition appeared equally often at each temporal place within a block. In addition, within each block of eight conditions, startle stimuli were presented in 50% of each condition (with no regard to the exact picture being presented), again in counterbalanced order across the blocks. Finally, four different sequences of blocks were constructed that were administered to equal numbers of participants in both parental history of hypertension groups. These procedures were applied in order to eliminate potential biases due to order of the conditions.

Statistical Analysis

The following statistical analyses were performed using the SPSS 11.5 statistical software package. Independent samples *t* tests and χ^2 tests were used to examine differences between PH− and PH+ groups on background variables. The effectiveness of the present modifications of the PRES technique was explored by examining its effects on the IBIs falling within the middle 3.3-s period of the 16 neutral baroreceptor manipulation trials. This middle period of the trials was selected because (a) it is the period during which the largest effects on IBI are expected (see Rau et al., 1992), and (b) it approximately covers the period of interest in the experimental trials, that is, the period between the onset of the picture and the startle probe. The mean of complete IBIs falling within this period was compared with the mean of complete IBIs falling in a 3.3-s period just preceding the trials. Analysis of variance for repeated measures was applied with IBI change from pre-PRES to during-PRES period as dependent variable, type of trial (baroreceptor stimulation vs. baroreceptor control) and medication (naltrexone vs. placebo) as within-subjects factor, and PH (PH+ vs. PH−) and gender as between-subjects factors. All tests were two-tailed using an alpha level of .05.

For tests regarding the main hypotheses, analysis of variance for repeated measures was applied including the following independent variables, all having two levels: mechanical baroreceptor condition (Pressure) × heart cycle phase (Phase) × picture valence (Valence) × naltrexone vs. placebo (Medication) × order of medication (Order) × PH Group (PH) × Gender. The first four variables are within-subject variables, and the last three variables are between-subjects variables. Because the groups were very similar in size, they were given equal weights in the analyses. Because of the multitude of effects tested, an alpha level of .01 (two-tailed) was applied here.

Translating the main hypotheses in statistical terms results in the following expected effects: (a) main effect of Pressure and/or a Pressure × Phase interaction effect on overall startle response magnitude, which was expected to be smaller during baroreceptor stimulation, (b) a Pressure × Valence, Phase × Valence, and/or Pressure × Phase × Valence interaction, reflecting smaller differences in startle eyeblink magnitude between conditions including positive versus negative pictures when baroreceptors are stimulated, (c) a Pressure × Valence, Phase × Valence, and/or Pressure × Phase × Valence interaction for subjective ratings of the pictures, demonstrating lower ratings of unpleasantness of negative pictures in the baroreceptor stimulation conditions, and (d) interactions of the aforementioned effects with PH, reflecting more pronounced effects in the PH+ group as compared to the PH − group. Mediation of the baroreceptor stimulation effects by opioids, if present, would be revealed by additional interactions with Medication.

Results

Baroreceptor stimulation trials (containing systolic suction and diastolic blowing) resulted in a mean IBI lengthening of 55.55 ms ($SD = 41.2$), from 838.49 ms ($SD = 125.84$) to 894.04 ms ($SD = 137.90$). In contrast, baroreceptor control trials (systolic blowing and diastolic suction) had no effect on IBI: $M = 834.13$ ms ($SD = 122.84$) before the trial and $M = 836.49$ ms ($SD = 118.59$) during the trial. The difference between the two kinds of trials regarding IBI change was highly significant, $F(1,74) = 106.87$, $p < .001$, $\eta^2 = .59$. This effect was not different for the two PH groups, $F(1,74) = 0.55$, $p > .10$, or medication sessions, $F(1,74) = 0.10$, $p > .10$, but it was somewhat more pronounced in men (mean IBI lengthening = 62.53 ms, $SD = 45.90$ in baroreceptor stimulation trials and $M = -4.36$, $SD = 27.45$ in baroreceptor control trials, $F[1,37] = 61.12$, $p < .001$) compared to women (mean IBI lengthening = 51.82, $SD = 45.53$ in baroreceptor stimulation trials and $M = 9.84$, $SD = 34.24$ in baroreceptor control trials, $F[1,37] = 46.40$, $p < .001$), the Baroreceptor Manipulation Trial Type × Gender interaction effect being small, but significant, $F(1,74) = 5.60$, $p < .05$, $\eta^2 = .07$.

Subjective Ratings of Pictures

As expected, negative pictures were rated as less pleasant ($M = 2.15$, $SD = 0.50$) than positive pictures ($M = 7.18$, $SD = 0.63$), $F(1,70) = 1857.70$, $p < .001$, $\eta^2 = .96$. Also, a Valence × Medication × Order interaction emerged, $F(1,70) = 22.17$, $p < .001$, $\eta^2 = .24$. Inspection of the means revealed that the interaction between the latter two factors reflected a session effect that moderated the effect of valence, making the difference between the ratings of negative and positive pictures somewhat more pronounced during the first session (Table 2). No other effects on subjective ratings of the pictures were found, including the hypothesized lower unpleasantness ratings of the negative pictures during baroreceptor stimulation, $Fs(1,70) < 1.00$, $p > .10$, for Pressure and Phase main effects, and Pressure × Phase, Pressure × Valence, Phase × Valence, and Pressure × Phase × Valence interactions.

Startle Responses

Startle eyeblink response magnitudes were lower in trials with positive pictures as compared to trials with negative pictures, $F(1,70) = 10.92$, $p < .001$, $\eta^2 = .14$. However, a Valence × Gender interaction, $F(1,70) = 7.46$, $p < .01$, $\eta^2 = .10$, also appeared, indicating that the valence effect was only present in men, $F(1,35) = 15.70$, $p < .001$, $\eta^2 = .31$, not in women, $F(1,35) = 0.20$, $p > .10$ (Figure 2).

Table 2. *Valence Ratings of the Pictures: Means and Standard Errors of the Mean*

	Negative Pictures	Positive Pictures
Order 1		
Session 1: Placebo	2.04 (0.08)	7.26 (0.09)
Session 2: Naltrexone	2.29 (0.08)	7.14 (0.11)
Order 2		
Session 1: Naltrexone	2.07 (0.09)	7.20 (0.11)
Session 2: Placebo	2.21 (0.09)	7.14 (0.10)

Note: A higher score reflects higher pleasantness.

A main effect of mechanical pressure showed a reduced startle response during negative pressure (suction), as compared with positive pressure (blowing), $F(1,70) = 12.85$, $p < .001$, $\eta^2 = .16$. This effect was strongest during the systolic phase of the heart cycle (maximum baroreceptor stimulation), as evidenced by a Pressure × Phase interaction, $F(1,70) = 8.11$, $p < .01$, $\eta^2 = .10$ (Figure 3). Tests of simple effects revealed that whereas the mechanical pressure effect was highly significant during systole, $F(1,70) = 21.16$, $p < .001$, $\eta^2 = .23$, it was not significant during diastole, $F(1,70) = 2.28$, $p > .10$. An inverse view of the interaction also holds: Only in the negative pressure condition did presentation of the startle probe during the systolic phase of the heart cycle result in significantly smaller eyeblink responses than during diastole, $F(1,70) = 9.41$, $p < .01$, $\eta^2 = .12$.

No other main or interaction effects were found, including those that addressed the hypotheses concerning baroreceptor stimulation effects (a) on modulation of startle responses by affective pictures, (b) being more pronounced in the PH+ group, and (c) being mediated by opioids. None of the interactions pertaining to the hypothesized baroreceptor stimulation effects on startle modulation was significant, $F(1,70) = 2.82$, $p = .10$, for the Pressure × Valence interaction (the trend was not in the hypothesized direction), and $Fs(1,70) < 1.00$, $p > .10$, for Phase × Valence and Pressure × Phase × Valence interactions. Because we found no overall modulation effects by the affective pictures in women, this analysis was also performed in men only. Results were similar to the analysis performed on the whole

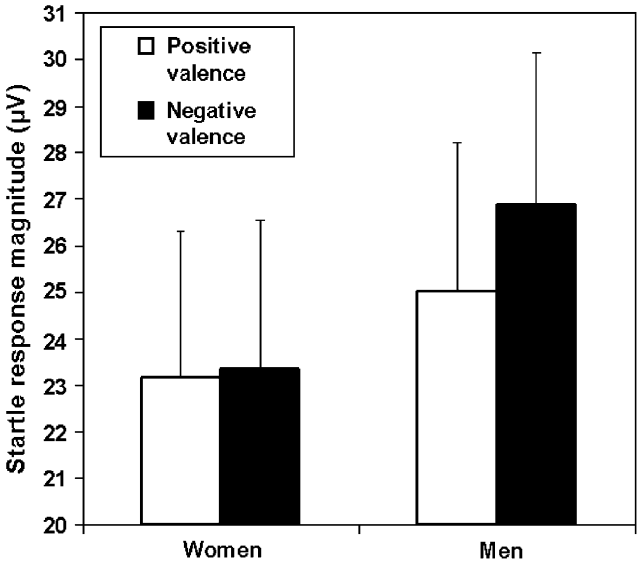

Figure 2. Startle response magnitude (in microvolts) after viewing pictures with a positive or negative valence in women and men. Depicted are means with the vertical lines representing standard errors.

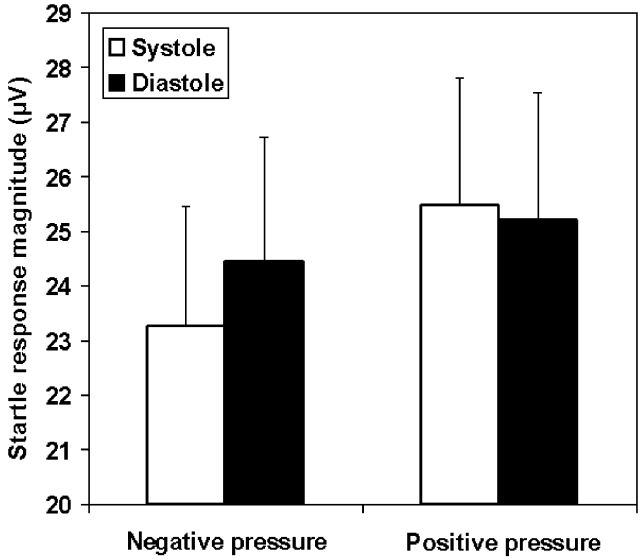

Figure 3. Startle response magnitude (in microvolts) during mechanical carotid baroreceptor manipulation (negative pressure = stimulation, positive pressure = inhibition) and natural baroreceptor conditions (stimulation during systole, inhibition during diastole). Depicted are means with the vertical lines representing standard errors.

sample, $F(1,35) = 2.60$, $p > .10$, for the Pressure × Valence interaction, and Fs$(1,35) < 1.00$, $p > .10$, for Phase × Valence and Pressure × Phase × Valence interactions.

No evidence was found for an enhanced baroreceptor effect on startle responses in offspring of hypertensives, Fs$(1,70) < 1.00$, $p > .10$, for all two-way and three-way interactions involving mechanical pressure, heart cycle phase, and PH. Neither did we find evidence for mediation of baroreceptor stimulation effects on the startle eyeblink response by opioids, $F(1,70) = 2.77$, $p = .10$, for Pressure × Medication (the trend not being in the hypothesized direction), and Fs$(1,70) < 1.00$, $p > .10$, for Phase × Medication and Pressure × Phase × Medication interactions.

Discussion

The first objective of the present study was to examine the effects of stimulation of carotid baroreceptors on startle reflex magnitude. When the startle stimulus was presented during negative cuff pressure (artificial stimulation of carotid baroreceptors), the startle response amplitude was significantly smaller than when the stimulus was presented during positive cuff pressure (inhibition of baroreceptor firing). In one previous study, using continuous (in contrast to phasic) neck cuff carotid stimulation, preliminary evidence was obtained for attenuated eyeblink responses during baroreceptor stimulation (Rau & Elbert, 2001). However, this stimulation technique may have resulted in confounding effects (due to differential auditory or tactile sensations associated with positive and negative cuff pressure). The present phasic PRES technique has been designed to circumvent such confounding effects. Furedy et al. (1992) have shown that most subjects cannot reliably differentiate whether sequences of heart-cycle-related cuff pressure changes constitute baroreceptor stimulation or control trials. This does not exclude the possibility that individual brief suction and blowing impulses were associated with different tactile or auditory sensations, potentially resulting in differential prepulse inhibition effects on startle response magnitude (Filion, Dawson, & Shell, 1998). However, we found that the effect of negative pressure was only significant during the systolic phase. Similarly, in the negative pressure condition, presentation of the startle probe during systole resulted in significantly smaller responses than presentation during diastole. These effects cannot be explained by differential prepulse inhibition effects. Rather, the effects strongly argue for the presence of synergistic effects of mechanical and natural baroreceptor stimulation on the startle eyeblink response. The present results extrapolate previous findings, showing carotid baroreceptor stimulation to attenuate responsiveness to painful stimuli (Dworkin et al., 1979; Rau & Elbert, 2001), to nonpainful aversive stimuli, that is, startling noise bursts.

Regarding modulation of the startle eyeblink response by preceding affective pictures, the first question is whether the 100-ms presentation time of the pictures is long enough for startle modulation. Men and women rated negative pictures as substantially more unpleasant than positive pictures. However, larger startle responses to unpleasant pictures were seen only in men. The affective modulation effect in men was even of a similar magnitude to that found in previous studies using long picture exposure times (Bradley et al., 1993; VanOyen Witvliet & Vrana, 1995; Vrana et al., 1988). Whether the present sex difference is due to selective effects of the very short picture exposure times on the sexes or to stronger attentional distraction by the PRES stimulation technique in women remains unknown at present. Globisch, Hamm, Esteves, and Öhman (1999) have found modulatory effects of unpleasant pictures using short presentation times (150 ms), which were not different for men and women and which were of a similar magnitude compared to the frequently used 6000-ms presentation time. However, the modulatory effect was found only in subjects highly fearful of spiders or snakes that were depicted on the slides. Because the nonfearful subjects rated the pictures of spiders and snakes as affectively neutral, the absence of a modulatory effect in this subgroup is not surprising. To our knowledge, the present results are the first to show affective startle modulation in nonfearful men, but not women, using such short picture presentation times.

No evidence was obtained for the hypothesized effect of baroreceptor stimulation on startle modulation by affective pictures, even when the analysis was confined to men. In addition, no support was obtained for our hypothesis that baroreceptor stimulation would diminish subjective ratings of aversiveness of negative pictures. In fact, baroreceptor stimulation had no effects on ratings of either negative or positive pictures. Together, our results suggest that carotid baroreceptor stimulation has a dampening effect on more basal responses to physical aversive stimuli like noise bursts, perhaps involving only a small number of lower brain stem nuclei in case of the auditory eyeblink response (Davis et al., 1982), rather than on affective processing of more complex aversive stimuli requiring the involvement of limbic structures such as the amygdala (Koch, 1999).

This conclusion may challenge the operant conditioning of hypertension hypothesis, which implies that affective responses to more complex stressors should also be attenuated by baroreceptor stimulation (Dworkin, 1988; Dworkin et al., 1979; Rau & Elbert, 2001). One could argue that viewing affective pictures in a laboratory setting is not ecologically valid with respect to processing of daily life stressors, which is considered central to the mechanism of operant conditioning of hypertension. As stated above, participants found the pictures clearly pleasant or unpleasant.

Nevertheless, future research on baroreceptor stimulation should focus on stressful stimuli that are more relevant to daily life of the participants. However, such stimuli would typically have a much longer duration than stimuli permitted in designs using the PRES technique (maximum 100 ms). Other baroreceptor stimulation techniques, permitting stimuli of a longer duration, such as the tilting table method (Vaitl & Gruppe, 1990), may be useful in studies with a higher ecological validity.

The baroreceptor stimulation effect on the startle response magnitude was not different for participants with or without a parental history of hypertension. This finding may also challenge the operant conditioning of hypertension hypothesis, because the dampening effects of the baroreceptors are hypothesized to be stronger in persons at risk for hypertension (Dworkin, 1988; Elbert et al., 1988; Rau et al., 1994). Alternatively, it may be postulated that the dampening effects of the baroreceptors are a risk factor independent of other risk factors for hypertension development, such as family history of hypertension. In some previous studies, baroreceptor dampening effects on pain sensitivity were indeed found to be independent of effects associated with family history of hypertension or elevated blood pressure (France et al., 1991; Rau et al., 1994).

The present results are in agreement with studies finding attenuating effects of baroreceptors on other basal reflexes, such as the Achilles tendon reflex (Dworkin et al., 1994) and the nociceptive flexion reflex (Edwards et al., 2003). Regarding the nociceptive flexion reflex, dampening effects were found of natural baroreceptor stimulation during systole, but no effects were obtained for mechanical baroreceptor stimulation by the PRES technique (Edwards et al., 2003). However, the absence of the latter effect may have been due to the fact that during the trials only a single suction or blowing stimulus with a relatively high intensity was applied. This procedure resulted in increased muscle tension, which may have masked any baroreceptor stimulation effects on the nociceptive flexion reflex. Nevertheless, the possibility cannot be ruled out that artificial and natural baroreceptor stimulation have somewhat different effects on different reflexes. For instance, mechanical baroreceptor stimulation has been found to attenuate the human Achilles tendon reflex (Dworkin et al., 1994), and recently no evidence was obtained for a dampening effect of natural baroreceptor stimulation on the stretch reflex in ankle extensor and flexor muscles (McIntyre, Ring, & Carroll, 2004). As the latter authors argued, this discrepancy may be due to quantitative differences in baroreceptor stimulation: the relatively stronger mechanical stimulation may be needed for attenuating non-nociceptive reflexes.

Opioid blockade did not influence the startle response. It may have been expected that opioid blockade would result in larger eyeblink responses due to the putative attenuating effects of opioids on anxiety (Sher, 1998). Anxiety has been found to enhance acoustic startle reflexes (e.g., Globisch et al., 1999). In a recent study (Fendt & Mucha, 2001), opiate withdrawal resulted in augmented fear-potentiated startles in mice. However, the design of that study was fundamentally different from the one employed in our study as it involved exogenous opiates, stimuli presented in the context of a fear-potentiation paradigm, and the whole-body startle response. Because eight subjects reported nausea to some degree in the present investigation, aspecific effects, such as distraction by nausea, might have disturbed any effects of opioid blockade in these subjects. However, when these participants were asked whether they thought the nausea distracted them from the task, they denied such an effect and excluding these participants from the analyses did not change the results.

Our primary question with regard to opioids was whether opioid blockade would diminish the effects of baroreceptor stimulation on the startle response magnitude. In pain studies, evidence for the role of opioids in hypertension- and baroreceptor-related antinociception has been equivocal (Bragdon et al., 2002; Bruehl et al., 2002; Maixner & Randich, 1984; Saavedra, 1981; Schobel et al., 1998; Zamir & Segal, 1979). This is the first study to investigate a potential mediating role of opioids in baroreceptor stimulation effects on responses to nonpainful aversive stimuli (noise bursts). Our data indicate that opioids are not involved in these effects. Which neurophysiological pathways are involved remains unclear at present. At the primary startle circuit level, mainly at the nucleus reticularis pontis caudalis, several neurotransmitters and peptides are known to be able to alter acoustic startle magnitude in rodents, such as GABA(A) (Meloni & Davis, 1999), corticotrophin releasing factor (Birnbaum & Davis, 1998), cyclic AMP (de Lima & Davis, 1995), and substance P (Kungel, Ebert, Herbert, & Ostwald, 1994). These substances are also known to have a reciprocal role in the cardiovascular baroreflexes (Bousquet, Feldman, Bloch, & Schwartz, 1982; Häusler & Osterwalder, 1980; Lewis & Coote, 1996; Redgate, 1968; Schmid, Palkovits, Muller, & Heidland, 1982). Future studies may focus on examining whether some of these substances are involved in a mechanism by which baroreceptor stimulation exerts its dampening effect on the acoustic startle magnitude.

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